

REMARKS

Reconsideration is requested.

The specification has been amended to include a cross reference to the noted U.S. provisional application and foreign applications. Attached is a new inventors' Declaration which includes a claim to benefit of PCT/JP01/08804 under 35 U.S.C. § 119, as the PCT application did not designate the U.S.

A Petition under 37 CFR § 1.78(a) and surcharge under 37 CFR § 1.17(t), as described by the Examiner on pages 2-4 of the Office Action dated February 13, 2004 (Paper No. 02022004), or anything further, is not believed to be required to comply with Rule 78. The Examiner is requested to see the attached Notice ("Claiming the Benefit of a Prior-Filed Application under 35 U.S.C. §§ 119(e), 120, 121, and 365(c)") dated February 24, 2003 from Stephen G. Kuhnin, Deputy Commissioner for Patent Examination Policy, as well as the applicants' Transmittal Letter of June 17, 2002 and the Patent Office Filing Receipt dated September 27, 2002, which includes a correct statement of the priority documents and their relationship to the above-identified U.S. application Serial No. 09/971,773.

Specifically, the attached Notice states the following in Part IV ("Office Practice to Not Require Petition and Surcharge if Benefit Claim is Not Present in the Proper Place But is Recognized By Office Continues But Applicants Are Advised That Proper Reference Must be Presented"):

"Previously the Office indicated that if an applicant includes a benefit claim in the application but not in the manner specified by 37 CFR 1.78(a) (e.g., if the claim is included in an oath or declaration or the application transmittal letter) within the time period set forth in 37 CFR 1.78(a), the Office

will not require a petition under 37 CFR 1.78(a) and the surcharge under 37 CFR 1.17(t) to correct the claim if the information concerning the claim was recognized by the Office as shown by its inclusion on the filing receipt. ... The Office will continue to follow this practice."

Certified copies and English language translations of the priority documents will be forwarded under separate cover.

The specification has been amended at page 4 in response to the Examiner's objection of the same at page 4 of Paper No. 02022004. The citation of the reference was readily determined from an internet search by the undersigned with Google and the information of the original disclosure. No new matter has been added.

Claims 35 and 62 have been canceled, without prejudice.

The withdrawn claims have been amended with an indication of their current status, as required by the PTO "REVISED AMENDMENT PRACTICE: 37 CFR 1.121 CHANGED COMPLIANCE IS MANDATORY - Effective Date: July 30, 2003" Flyer (Rev. 3 (07/24/03)). See, specifically Example 8 of the Flyer.

Claims 64-68 have been added. Support for new claims 65 and 67 may be found, for example, in the paragraph bridging pages 48 and 49 of the specification. Support for new claims 66 and 68 may be found, for example, in the first full paragraph on page 81 of the specification. No new matter has been added.

Figure 22 has been amended in the attached formal drawings to include SEQ ID NOs: 11 and 12, in place of the originally-filed Figure 22 which recited SEQ ID NOs: 8 and 9, based on the description of page 162 of the specification. A hand-written marked-up copy of originally-filed Figure 22 is attached wherein the change has been

indicated. No new matter has been added. The Examiner is requested to advise the undersigned if anything further is required in this regard.

Claims 2, 3, 20-22, 24-30 and 41-61 have been withdrawn from consideration. The Examiner has indicated that claims 1, 4, 12-19, 23, 31-40 and 62-64 are under active consideration. Claims 5-11 and 24-30 however "will be rejoined for consideration, along with the non-elected species upon allowance of all the elected subject matter." See, page 2 of Paper No. 02022004. The applicants also however request rejoinder of claims 2, 3 and 20, which are not believed to be patentably distinct from the subject matter of the Examiner's Group II of the Office Action dated June 17, 2003 (Paper No. 13). Specifically, the Examiner has asserted in Paper No. 13 that "the CHO cells of group I [as defined by claims 1-3 and 20] have a normal activity of an enzyme relating to the synthesis of an intracellular nucleotide GDP-fucose and/or relating to the modification of a sugar chain, whereas the activity of such enzyme is decreased or deleted in the CHO cells of group II [as defined by claims 1, 4-19 and 23-40]." See, pages 4-5 of Paper No. 13.

The applicants note however that the subject matter of the Examiner's Groups I and II have been defined by the Examiner in the same Class and Subclass (i.e., Class 435, Subclasses 69.1 and 455) such that examination of the subject matter of the Examiner's Group II (i.e., the elected subject matter) and the subject matter of the Examiner's Group I (i.e., as defined by claims 1-3 and 20) will necessarily require a review of the same art.

Moreover, the indication by the Examiner that the subject matter of the Examiner's Groups I and II are defined by the same Class and Subclasses is strong

evidence that the subject matter of the examiner's Groups I and II have not been established as distinct in the art, which would otherwise require separate classification by the Patent Office. Restriction is not believed to be appropriate.

Finally, the applicants note in this regard that claim 1 has been indicated by the examiner as being defined by both of the Examiner's Groups I and II and has been examined. Claim 4 (of Group II), like claims 2 and 3 and 20 (of Group I), is dependent from claim 1. None of claims 2, 3 or 20 specify that the claimed CHO cells have a normal activity of an enzyme relating to the synthesis of an intracellular nucleotide GDP-fucose and/or modification of a sugar chain, to the exclusion of the decreased or deleted activity of an enzyme relating to the synthesis of an intracellular nucleotide GDP-fucose, which is the Examiner's stated basis for requiring restriction between the Examiner's Groups I and II. In fact, claim 2 further defines the CHO cell of claim 1 as producing an antibody composition wherein the sugar chain to which fucose is not bound is a complex N-glycoside-linked sugar chain in which fucose is not bound in the 6-position of N-acetylglucosamine in the reducing end. The Examiner's basis for requiring restriction between the subject matter of the Examiner's Groups I and II is not believed to reflect the claimed subject matter.

Clarification, or examination of the subject matter of the Examiner's Groups I and II, is requested.

Examination of all of the pending claims, or an indication that the pending claims will be considered upon allowance of the elected subject matter, is requested.

The Section 112, second paragraph, rejection of claims 4 and 12-19 stated on page 5 of the Office Action dated February 13, 2004, is obviated by the above

amendments. Claim 4 has been amended to recite an amount of "activity of an enzyme relating to the modification of a sugar chain in which fucose is bound to the 6-position of N-acetylglucosamine in the reducing end through $\alpha(1\rightarrow6)$ glycosyl bond in the complex N-glycoside-linked sugar chain must be decreased." See, page 5 of the Office Action dated February 13, 2004. Specifically, claim 4 recites that the activity of an enzyme relating to the modification of a sugar chain in which fucose is bound to 6-position of N-acetylglucosamine in the reducing end through $\alpha(1\rightarrow6)$ glycosyl bond in the complex N-glycoside-linked sugar chain is decreased to the extent that the CHO cell will be resistant to a lectin which recognizes a sugar chain in which fucose is bound to the 6-position of N-acetylglucosamine in the reducing end through an $\alpha(1\rightarrow6)$ glycosyl bond in the complex N-glycoside-linked sugar chain. The specification teaches that resistance to such a lectin is related to decreased activity of the recited enzyme. The Examiner is requested to see, for example, Example 14 of the specification in this regard.

Withdrawal of the Section 112, second paragraph, rejection of claims 4 and 12-19 stated on page 5 of the Office Action dated February 13, 2004, is requested.

The Section 112, second paragraph, rejection of claims 23 and 31-40 stated on pages 5-6 of the Office Action dated February 13, 2004, is similarly believed to be obviated by the above amendments. Claims 23 has been amended above in manner similar to claim 4 discussed above. As the Examiner's comments in rejecting claims 23 and 31-40 are similar to the Examiner's comments rejecting claims 4 and 12-19, the Examiner is requested to see the above comments relating to claims 4 and 12-19. Claims 23 and 31-40 are submitted to be definite. Withdrawal of the Section 112, second paragraph, rejection of claims 23 and 31-40 is requested.

The Section 112, second paragraph, rejection of claim 19 is obviated by the above amendments. Withdrawal of the rejection is requested.

The Section 112, second paragraph, rejection of claim 62 is moot in view of the above.

The Section 112, second paragraph, rejection of claim 63 is obviated by the above amendments. Claim 63 is submitted to be definite and withdrawal of the Section 112, second paragraph, rejection of claim 63 is requested.

The Section 112, first paragraph, rejection of claims 1, 4, 12-19, 23, 31-40 and 62-64 is traversed. Reconsideration and withdrawal of the rejection are requested in view of the following as well as the attached.

The Examiner's indication that the specification is

"enabling for a CHO cell comprising a deletion of at least exon 2 of one FUT8 gene, which deletion produces a non-functional enzyme, into which a gene encoding an antibody is introduced, such antibody gene being expressed and producing antibodies having complex N-glycoside-linked sugar chains bound to the Fc region, wherein among the total complex N-glycoside-linked sugar chains bound to the Fc region in the composition, the ratio of a sugar chain in which fucose is not bound to N-acetylglucosamine at the 6 position is 20% or more"

is acknowledged, with appreciation. See, page 7 of the Office Action dated February 13, 2004. The applicants respectfully submit however that the specification teaches more than the exemplified embodiments which appear to be the extent of the subject matter which the Examiner believes is enabled by the description. In fact, the state of the art in the field of, for example, genetic manipulation techniques, at the time of the present invention, were quite advanced. Moreover, the knowledge in the art relating to antibody production from CHO cells, manipulation of CHO cells and enzymes relating to

the synthesis of an intracellular sugar nucleotide, GDP-fucose and/or modification of a sugar chain in which fucose is bound to the 6-position of N-acetylglucosamine in the reducing end through an $\alpha(1\rightarrow6)$ glycosyl bond in a complex N-glycoside-linked sugar chain, were advanced at the time of the present invention.

The applicants exemplified the presently claimed Invention by producing a cell in which a gene encoding an antibody molecule was introduced into a CHO cell having a decreased or deleted enzyme activity of $\alpha 1,6$ -fucosyltransferase as the host cell. As noted above, the Examiner appears to have accepted that the specification teaches one of ordinary skill in the art how to make and use a CHO cell in which the exon 2 of a gene encoding $\alpha 1,6$ -fucosyltransferase is deleted in order to delete the enzyme activity of $\alpha 1,6$ -fucosyltransferase of the cell. The Examiner appears to believe the applicants have not taught how to make and use cells in which a gene in another region is destroyed, for example.

The applicants submit however, that one of ordinary skill in the art would have been able to prepare a cell in which the enzyme activity of $\alpha 1,6$ -fucosyltransferase, for example, is deleted or decreased without limitation to the exon 2, based on the present specification. The Examiner is requested to consider the attached in this regard, with the following discussion.

One of ordinary skill in the art will appreciate that in order to obtain a knock-out cell, the intron and exon structures of the target gene should be, advantageously, recognized. One of ordinary skill in the art would appreciate the intron and exon structures of, for example, $\alpha 1,6$ -fucosyltransferase, by using a method similar to the method described in Example 12 of the present specification, if the cDNA of the target

gene is known. The following references (copies of which are attached) describe that the relevant structures can be determined based on the cDNA:

- (i) Glycobiology, vol.9, 323-334 (1999) and
- (ii) Glycobiology, vol.8, 87-94 (1998).

In reference (i), the structure motif which is important to the activity of the fucosyltransferase was expected from fucosyltransferases derived from various species (see Figs. 2, 3, 4 and 6). In the reference (ii), the structure which is important to the activity of the fucosyltransferase was similarly expected (Fig. 3).

As for the region of the gene to be deleted, one of ordinary skill will appreciate that after the determination of the structure, any region can be deleted, so long as the activity of the gene is deleted. Generally, one of the ordinary skill in the art would delete the following regions.

- (1) ATG site,
- (2) promoter region, and/or
- (3) active site of protein.

The deletion of these region is apparent for one of ordinary skill in the art based on the following references (copies of which are attached), for example:

- (iii) The EMBO Journal, vol.16, 1850-1857, (1997), and
- (iv) Cell, vol.86, 643-653, (1996)

In reference (iii), the exon I containing ATG of β 1,4-galactosyltransferase is deleted to prepare a knock-out mouse (p. 1851, right column, Fig. 1A). Also, in the reference (iv), the region containing a catalyst domain of fucosyltransferase VII is deleted (p. 644, right column, Fig. 2A).

The inventors of the presently claimed invention found cDNA encoding $\alpha 1,6$ -fucosyltransferase in CHO cells and the exon 2 genomic region, as described in Example 12 of the present specification. Since the exon 2 contains ATG site, this selection was carried out according to ordinary, well-known methods in the production of knock-out cells. It will be apparent for one of ordinary skill in the art that a knock-out cell could be prepared, without an undue amount of experimentation, by deleting, for example, regions containing an ATG site, a promoter region, and/or an active site of a protein of interest in addition to or in place of the exon 2 region exemplified in the present application.

The claims are submitted to be supported by an enabling disclosure and withdrawal of the Section 112, first paragraph, rejection of claims 1, 4, 12-19, 23, 31-40 and 62-64 is requested.

The Section 102 rejection of claim 1 over Lifely et al ((1995) Glycobiology 5(8): 813-22) is traversed. Reconsideration and withdrawal of the Section 102 rejection of claim 1 are requested as the cited reference discloses sugar chain analysis data of an antibody produced by CHO cells in Figure 3A. There are five (5) kinds of sugar chains detected in the cited art, as described by peaks 004300, 004301, 014-00, 004300 and 014300. The areas of peaks 004300 and 014300 based on the total are calculated to be less than 20%. As the cited art fails to teach each and every aspect of claim 1, claim 1 is submitted to be patentable over the cited art. Withdrawal of the Section 102 rejection of claim 1 is requested.

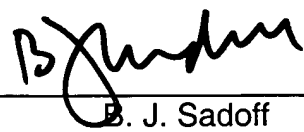
KANDA, et al.
Appl. No. 09/971,773
August 12, 2004

The claims are submitted to be in condition for allowance and a Notice to that effect, along with further rejoinder and allowance of the above-noted claims, are requested.

The Examiner is requested to contact the undersigned in the event anything further is required.

Respectfully submitted,

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Marked-up copy of
Proposed Amended
Figure

FIG. 22

